Case Report/Case Series

Concurrent Vismodegib and Radiotherapy for Recurrent, Advanced Basal Cell Carcinoma

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IMPORTANCE Vismodegib is a targeted agent recently approved for treating patients who develop recurrent or locally advanced basal cell carcinoma (BCC), and will inevitably be integrated into existing therapy for advanced BCC as it becomes increasingly used. Improved understanding of how vismodegib interacts with other treatment modalities, including radiotherapy, would help optimize multidisciplinary therapy and clinical outcomes.

OBSERVATIONS We report 2 cases of recurrent, advanced BCC treated from April 1, 2012, through October 31, 2014, with concurrent radiotherapy and vismodegib. Concurrent treatment appeared to be well tolerated and efficacious, with both patients having no evidence of progressive disease at last follow-up.

CONCLUSIONS AND RELEVANCE We found that the combination of vismodegib and radiotherapy is feasible for patients with recurrent or locally advanced BCC and that combined use of currently available therapies for advanced BCC warrants further prospective study.

A
lthough surgical resection is curative in most patients with basal cell carcinoma (BCC), recurrent or more advanced disease may be treated with a combination of surgery and radiation. Cisplatin is sometimes used for patients with metastatic BCC, but no systemic therapy was approved for the treatment of BCC until recently with the advent of vismodegib. Response rates to systemic vismodegib were 30% and 43% for patients with metastatic and locally advanced BCC, respectively, with a median duration of response of 7.6 months.

As vismodegib becomes increasingly used, it will be important to address how to best integrate this new agent into existing therapy for advanced BCC. Improved understanding of how vismodegib interacts with radiation in this disease would help determine the optimal timing and sequencing of these various treatment modalities to enhance response rate and progression-free survival. Only one case of radiotherapy with vismodegib has previously been reported for the treatment of squamous cell carcinoma. We report the treatment of 2 cases of recurrent head and neck BCC using this novel combination of vismodegib and concurrent radiotherapy.

Report of Cases

With institutional review board approval of Stanford University, a search of patients who received vismodegib and concurrent radiotherapy was conducted. Two patients were identified as having been treated with vismodegib and concurrent radiotherapy from April 1, 2012, through October 31, 2014. Treatment-related toxic effects were classified according to the Common Terminology Criteria for Adverse Events.

Case 1

A man in his 60s presented with a left nasal tip BCC that was initially treated with Mohs surgery. Although this lesion had received no prior treatment and his surgery revealed no aggressive features, he developed pain and numbness 10 months later in the V2 distribution of the left cranial nerve and was initially medically managed for trigeminal neuralgia. However, his symptoms progressed during the next 3.5 years. He was ultimately evaluated and found to have left cranial nerve V1 to V3, VI, and VII palsies on examination. Concern was raised for perineural spread of the tumor that involved left cranial nerve V1 to V3, VI, and VII and the left cavernous sinus on skull base magnetic resonance imaging (MRI). Biopsy of the left V2 nerve confirmed BCC with perineural invasion. Positron emission tomography–computed tomography revealed no distant disease. He was prescribed vismodegib, 150 mg/d, with concurrent radiotherapy. The clinical area of the disease, which included the left infraorbital nerve, left cranial nerves V2, V3, and VII (including greater superficial petrosal and auriculotemporal nerve), left Meckel cave, and cavernous sinus, was treated with 66 Gy in 33 fractions. The left infratemporal fossa and parotid were treated with 50 Gy in 33 fractions. Volumetric modulated arc technique with image guidance and 6-MV...
photonswereused.Thepatientdevelopedgrade1dermatitis
andgrade1mucositisduringradiotherapybutwasableto
complete the full course of treatment without any breaks, and his
pain improved by midtreatment. He continued to take vismo-
degib for an additional 3 months after radiotherapy but stopped
taking it because of taste changes, loss of appetite, muscle
cramping, and fatigue. With a follow-up of 9 months, including
MRI every 3 months, he had stable disease apparent on
imaging, had improvement in his left facial weakness, and con-
tinued to be pain free (Figure 1).

Case 2
A man in his 70s presented with a left lower eyelid and lateral
canthal BCC that was initially treated with Mohs surgery. Three
years later, he developed diplopia and a new mass over the left
lateral canthus at the site of his previous left lower lid recon-
struction. Computed tomography of the orbit revealed thick-
ening that measured 6.5 × 7.4 mm in the region of the left lower
eyelid and lateral canthus, and left orbital biopsy revealed in-
filtrative BCC. The patient opted for treatment with vismo-
degib, 150 mg/d, to try to shrink the lesion before resection. Af-
fter 2 months of vismodegib therapy, the patient underwent an
MRI of the orbit, which again revealed a left lateral orbital le-
sion, which measured 6.3 × 5.6 mm. He underwent a left globe-
sparing resection with positive margins, followed by adjuvant
radiotherapy, while continuing to take vismodegib. The radio-
therapy target volume, which encompassed the postoperative
bed at the left lateral orbit, was treated to a total dose of 51 Gy
in 17 fractions using mixed 6-MeV and 9-MeV electrons. This ra-
diotherapy schedule was chosen after discussion with the pa-
tient and consideration of his social and transportation issues.
He developed grade 1 dermatitis in the radiation field during his
radiotherapy. He stopped taking vismodegib 2 weeks after
completion of radiotherapy because of increased fatigue, weight
loss, and shortness of breath. With a follow-up of 12 months, in-
cluding posttreatment MRI and regular ophthalmologic evalu-
ations, he continues to be disease free, with dry eye managed
by eye drops as his only radiation-associated toxic effect. The
left globe and lacrimal gland received mean doses of 12.5 and
22.3 Gy, respectively. Before radiation, his left eye vision with-

Figure 1. Pretreatment and Posttreatment Magnetic Resonance Imaging (MRI), Pretreatment Positron Emission Tomography (PET),
and Radiotherapy Plan for Patient 1

A, Pretreatment PET showing increased uptake in the left infraorbital foramen
(white arrow). B, Pretreatment T1 postcontrast MRI showing enhancement of
the left cranial nerve V3 through the foramen ovale in a coronal section of the
skull base (white arrow). C, Pretreatment T1 postcontrast MRI showing
enhancement of the preoptic cistern component of left cranial nerves VI
(white arrow) and V (red arrow) in an axial section of the skull base.

D, Radiotherapy plan with 66-Gy (magenta), 60-Gy (blue), and 40-Gy (cyan)
isodose lines. E, Posttreatment T1 postcontrast MRI showing stable to
decreased enhancement of left cranial nerve V3 in a coronal section of the
skull base. F, Posttreatment T1 postcontrast MRI showing stable to decreased
enhancement of left cranial nerves V and VI in an axial section of the skull base.

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Discussion

Vismodegib, an exciting advance in the treatment of advanced BCC, with 30% to 60% objective responses reported,\textsuperscript{3,5-7} is effective for patients with metastatic or locally advanced BCC who are not candidates for or who have had disease recurrence after surgery and/or radiation therapy. However, there are limitations to this drug because treatment duration can be limited by adverse effects, including muscle spasms, alopecia, dysgeusia, weight loss, and fatigue. Acquired resistance to Hedgehog pathway inhibition after initial response is also an increasing concern.\textsuperscript{8} In addition, cases of vismodegib-associated squamous cell carcinoma within and distant to BCC have been reported.\textsuperscript{9-11}

There has been great interest in expanding the use of vismodegib and using it not just as monotherapy but as an adjunct to existing treatments. Vismodegib therapy is being explored in the neoadjuvant setting in an attempt to reduce tumor volumes to facilitate resection\textsuperscript{12,13} or radiotherapy and even in the concurrent setting with radiotherapy.\textsuperscript{14} The interaction between radiotherapy and Hedgehog pathway inhibition has not been well studied, but available preclinical data support combining vismodegib with radiotherapy. Stimulation of Hedgehog signaling has been reported to reduce radiosensitivity in hepatocellular carcinoma,\textsuperscript{15} and inhibition of Hedgehog signaling in an esophageal cancer cell line was reported to increase radiosensitivity.\textsuperscript{16} Zeng et al\textsuperscript{17} found that although Hedgehog pathway inhibition did not alter radiosensitivity in vitro, it enhanced radiosensitivity in their in vivo non-small cell lung cancer models, suggesting that this effect may be mediated through paracrine stromal signaling. Although vismodegib’s potential for radiosensitization and synergistic efficacy with radiotherapy is promising, there is also concern for potential synergistic toxic effects.

There is scarce clinical experience to guide us on using vismodegib with concurrent radiotherapy for BCC. There has been one case report of a patient who was taking vismodegib for BCC and then developed left parietal and left zygomatic squamous cell carcinomas, which were successfully treated with radiotherapy while continuing vismodegib treatment.\textsuperscript{4} We are the first, to our knowledge, to report the treatment of BCC using concurrent radiotherapy and vismodegib. Concurrent treatment appeared to be well tolerated and efficacious, with both patients having no evidence of progressive disease at last follow-up, despite discontinuing vismodegib treatment because of adverse effects and not using any subsequent therapy. Even though proximity to normal structures can limit the use of radiotherapy in advanced BCC, both patients completed radiotherapy without significant adverse effects.

Conclusions

It can be difficult to determine optimal therapy for this heterogeneous and complex patient population with advanced BCC. Treatment should continue to be multidisciplinary, with consideration of local and systemic therapy, so that this patient population with a poor prognosis can be treated aggressively. We found that the combination of vismodegib and radiotherapy is feasible for these patients, and combined use of currently available therapies for advanced BCC warrants further prospective study.
responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Pollom, Colevas, Hara. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Pollom, Hara. Critical revision of the manuscript for important intellectual content: Bui, Chang, Colevas, Hara. Administrative, technical, or material support: Bui. Study supervision: Pollom, Chang, Colevas, Hara.

Conflict of Interest Disclosures: None reported.

REFERENCES


